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Original Research Article

Role Of SGLT2 Inhibitors in Slowing Progression of Chronic Kidney Disease Beyond Diabetes.

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Abstract: ***Background***: Chronic kidney disease (CKD) is a gradual disorder that eventually results in kidney failure, thus requiring dialysis or transplantation. The treatment development has happened, but it is not easy to stop the CKD development. SGLT2 inhibitors, which were created to treat diabetes, have been considered as the possible agents to help slow down CKD progression, even in non-diabetic patients. ***Objectives*** to evaluate the efficacy of SGLT2 inhibitors in the slower development of CKD in non-diabetic patients using kidney, albuminuria, blood pressure, and cardiovascular outcomes as outcome measures. ***Methodology*** It was a Cross-Sectional Observational Study. that lasted 12 months it involved 150 patients (non-diabetic) with CKD. SGLT2 inhibitors or a placebo were randomly applied to the participants. Their main outcome measure was the change in estimated glomerular filtration rate (eGFR), and the secondary outcomes were the albuminuria levels, blood pressure, and cardiovascular events. Baseline, 3-, 6-, and 12-months measurements were done. ANOVA and chi-square tests were used to analyze the data statistically, where a level of significance was identified as $p<0.05$, as data were continuous and categorical, respectively. ***Results*** Of the 150 enrolled participants, the mean age was 62.3 years (SD 8.4), with 60% male. Baseline eGFR averaged 45.7 mL/min/1.73m² (SD 9.2), and albuminuria levels were 300 mg/g. After 12 months, the SGLT2 inhibitor group showed a significant improvement in eGFR compared to the placebo group, with a mean difference of 5.2 mL/min/1.73m² ($p<0.01$). Albuminuria decreased by 30% in the treatment group, while it increased by 5% in the placebo group ($p<0.01$). Systolic blood pressure reduced by a mean of 6 mmHg in the treatment group, compared to 2 mmHg in the placebo group ($p=0.03$). Cardiovascular events, including hospitalizations due to heart failure, were reduced by 25% in the SGLT2 inhibitor group. No significant adverse events were noted, and both groups had comparable tolerability. ***Conclusion*** In non-diabetic patients SGLT2 inhibitors are important as they reduce the progression of CKD through enhancement of eGFR, reduction in albuminuria, and alleviation of blood pressure. The results indicate the potential of SGLT2 inhibitors as a useful intervention in treating CKD outside diabetes and potentially postponing the need for dialysis and leading to a better long-term patient outcome.

Keywords: CKD, SGLT2 inhibitors, eGFR, albuminuria

INTRODUCTION

Chronic Kidney Disease (CKD) is a disease that causes a progressive failure of the kidney as it ages, and this may result in end-stage renal disease (ESRD), where dialysis or kidney transplantation is required [1]. It is a significant health concern on the planet, and millions of individuals have been infected. It is estimated that there are 697.5 million individuals with CKD across the world in 2017, and as the population grows older and the prevalence of risk factors, such as diabetes, high blood pressure, and obesity, CKD is set to keep increasing. Conventionally, diabetes and hypertension have been strongly linked with CKD, yet a growing body of evidence indicates that the

condition may develop without considering these comorbidities [2,3].CKD is synonymous with a progressive reduction in the renal functional capacity estimated by the estimated glomerular filtration rate (eGFR) and is commonly accompanied by a rise in albuminuria (presence of albumin in the urine), which is an indicator of kidney damage [4]. In the long run, when the kidney activity reduces, dialysis or a kidney transplant operation can be necessary for the patient. This development is caused by a number of factors, such as genetic, lifestyle, and comorbid conditions, yet it can be altered through proper interventions [5].The recent developments in pharmacological therapy have brought new opportunities in the process of slowing down CKD progression. The SGLT2 inhibitors (sodium-glucose co-transporter 2 inhibitors) have been the most promising of these treatments. SGLT2 inhibitors have originally targeted the treatment of type 2 diabetes, but have been demonstrated to deliver more than glucose-reducing effects on the kidney as well [6]. The mechanism of action is inhibition of the SGLT2 protein in the proximal renal tubule to inhibit glucose reabsorption and promote its excretion through the urine. Nevertheless, a recent clinical trial has shown that SGLT2 inhibitors may also be used to offer direct renal protection, to lower albuminuria, and stabilize kidney function even in patients who do not have diabetes [7].The use of SGLT2 inhibitors in CKD has been considered in several studies, especially in diabetic nephropathy patients. Non-diabetic CKD patients, however, are an area of active study into their effects. The utility of SGLT2 inhibitors in this group of the population could be explained by their potential impact on glomerular hyperfiltration, reduction of blood pressure, decreased albuminuria, and direct anti-inflammatory and anti-fibrotic effects on the kidneys. In the face of the increased prevalence of CKD around the world, and particularly in non-diabetic people, there is clinical importance in determining the efficacy of SGLT2 inhibitors in reducing the progression of CKD in non-diabetic patients [8,9].The proposed study will aim at estimating the efficacy of SGLT2 inhibitors in non-diabetic patients with CKD. It pays attention to a number of the most important outcomes, such as kidney function (eGFR), albuminuria, and blood pressure, as well as the effect on cardiovascular health. The paper will also examine how SGLT2 inhibitors are likely to delay dialysis or kidney transplantation, which will eventually enhance the quality of life of the patient with CKD [10].

Study Objectives

The hypothesis of the study is to determine the effects of SGLT2 inhibitors on CKD development in non-diabetic patients, in particular, kidney function, albuminuria, blood pressure, and cardiovascular outcomes.

MATERIALS AND METHODS

Study Design & Setting

This Cross Sectional Observational Study Conducted Department of Nephrology Institute of kidney disease Peshawar from jan 2024 to jan 2025

Participants

Patients without diabetes who had CKD were enrolled in the study (150 patients). The study involved participants in the age group of 40-75 years, and an eGFR of 30-60 mL/min/1.73m 2 and an albuminuria level exceeding 200 mg/g. Others had very serious cardiovascular disease, malignancy, severe liver disease, or pregnancy. Informed consent was obtained from all the participants, and medical history was screened to include in the study.

Sample Size Calculation

The calculation of the sample size was conducted on the basis of the difference in eGFR per 5 ml/min/1.73m 2 between the treatment and the placebo groups; power of 80 and alpha level = 0.05. Based on these parameters, 150 participants (75 in each group) were needed to have statistical significance.

Inclusion criteria

Inclusion criteria: Adults aged between 40 and 75 years, non-diabetic, eGFR between 30 and 60 mL/min/1.73m 2, and albuminuria of more than 200 mg/g.

Exclusion criteria

Myocardial infarction/heart failure, active malignancy, severe liver disease, pregnancy, or some other disorders that may confound drug intake or study efficacy.

Diagnostic and Management Plan

The diagnosis of CKD was conducted using clinical assessment, laboratory results (eGFR, albuminuria), and radiograph. The management encompassed the standard CKD treatment, which consisted of controlling blood pressure, as well as randomly assigning either SGLT2 inhibitors or a placebo throughout the course of the study.

Statistical Analysis

The analysis of the data was performed with the help of SPSS software. ANOVA was used to compare continuous variables, whereas chi-square tests were used to evaluate categorical variables. The p-value of less than 0.05 was taken as statistically significant. The main endpoint (eGFR change) and the secondary endpoints (albuminuria, blood pressure) were compared regarding differences between groups.

RESULTS

150 participants were enrolled in the study, with 75 assigned to the SGLT2 inhibitor group and 75 to the placebo group. The mean age of participants was 62.3 years (SD 8.4), with 60% male. Baseline eGFR was 45.7 mL/min/1.73m² (SD 9.2), and albuminuria levels averaged 300 mg/g. After 12 months, the SGLT2 inhibitor group showed a significant improvement in eGFR, with a mean difference of 5.2 mL/min/1.73m² ($p<0.01$) compared to the placebo group. Albuminuria decreased by 30% in the treatment group, while it increased by 5% in the placebo group ($p<0.01$). Blood pressure reduction was more significant in the SGLT2 inhibitor group, with a mean reduction of 6 mmHg, compared to 2 mmHg in the placebo group ($p=0.03$). Cardiovascular events, including hospitalizations due to heart failure, were reduced by 25% in the treatment group. Both groups tolerated the treatment well, with no significant adverse events reported.

Intervention Outcome

The SGLT2 inhibitor group had a significant increase in eGFR, albuminuria, and blood pressure compared to the placebo group. These results indicate that SGLT2 inhibitors may be useful in delaying CKD development in non-diabetic patients and may promote the delay of dialysis, as well as enhance renal and cardiovascular outcomes.

Table 1: Baseline Characteristics of Study Participants

Characteristic	SGLT2 Inhibitor Group (n=75)	Placebo Group (n=75)
Age (years)	62.2 ± 8.3	62.4 ± 8.5
Male (%)	60%	60%
Baseline eGFR (mL/min/1.73m²)	45.6 ± 9.1	45.8 ± 9.3
Baseline Albuminuria (mg/g)	298 ± 58	302 ± 64
Systolic Blood Pressure (mmHg)	137.4 ± 14.5	138.0 ± 13.7

This table shows the baseline characteristics of participants in both the SGLT2 inhibitor and placebo groups. There were no significant differences between the groups at baseline.

Table 2: Change in eGFR After 12 Months

Group	Baseline eGFR (mL/min/1.73m²)	12-Month eGFR (mL/min/1.73m²)	Change in eGFR (mL/min/1.73m²)
SGLT2 Inhibitor Group (n=75)	45.6 ± 9.1	50.8 ± 10.3	+5.2 ± 2.1
Placebo Group (n=75)	45.8 ± 9.3	45.9 ± 9.4	+0.1 ± 0.5

This table presents the change in eGFR after 12 months of treatment with either SGLT2 inhibitors or placebo. The SGLT2 inhibitor group showed a significant improvement in eGFR compared to the placebo group ($p<0.01$).

Table 3: Change in Albuminuria After 12 Months

Group	Baseline Albuminuria (mg/g)	12-Month Albuminuria (mg/g)	Change in Albuminuria (%)
SGLT2 Inhibitor Group (n=75)	298 ± 58	208 ± 53	-30%
Placebo Group (n=75)	302 ± 64	317 ± 72	+5%

This table displays the changes in albuminuria after 12 months of treatment. The SGLT2 inhibitor group showed a significant decrease in albuminuria, while the placebo group had a slight increase ($p<0.01$).

Table 4: Change in Blood Pressure After 12 Months

Group	Baseline Systolic BP (mmHg)	12-Month Systolic BP (mmHg)	Change in BP (mmHg)
SGLT2 Inhibitor Group (n=75)	137.4 ± 14.5	131.4 ± 13.2	-6.0 ± 3.2
Placebo Group (n=75)	138.0 ± 13.7	136.0 ± 14.3	-2.0 ± 2.7

This table illustrates the change in systolic blood pressure after 12 months. The SGLT2 inhibitor group experienced a great reduction in blood pressure compared to the placebo group ($p=0.03$).

DISCUSSION

The results of the study contribute to the accumulating evidence to support the renoprotective action of sodium glucose co-transporter 2 (SGLT2) inhibitors in chronic kidney disease (CKD) patients regardless of the presence or absence of diabetes. Our findings, which indicate a substantial increase in estimated glomerular filtration rate (eGFR), a decrease in albuminuria, and a more massive decrease in systolic blood pressure, are consistent with various studies and meta-analyses that have been carried out during the last five years. These comparisons allow us to place our findings in the changing paradigm where SGLT2 inhibitors serve as the basis of CKD therapies other than glucose-lowering [11,12]. Big randomized controlled trials, especially DAPA CKD, have shown that dapagliflozin reduces the risk of progression of kidney disease and composite renal outcomes in patients with CKD with or without type 2 diabetes by a significant margin [13]. In particular, the DAPA CKD trial mentioned the decrease in the probability of the sustained reduction of eGFR, end-stage kidney disease (ESKD), or renal or cardiovascular mortality, and the same effect was observed in those who did not have diabetes [14. These findings are similar to the eGFR enhancement observed in our cohort and emphasize the wide applicability of the SGLT2 inhibition [15]. Likewise, the findings are also supported by the EMPA KIDNEY trial, which demonstrated that empagliflozin delays the progression of CKD and displays better cardiovascular outcomes, irrespective of diabetes status [16]. Further, EMPA KIDNEY subgroup analyses have indicated an advantage even in patients without major albuminuria, as our study showed albuminuria reduction, but again by different amounts depending on the baseline proteinuria [17]. Recent meta-analyses of clinical trials have measured the total effect of SGLT2 inhibitors, which is estimated at being approximately 30-40 percent risk reduction of CKD progression, further supporting the idea that the favorable impact of renal outcomes of SGLT2 inhibitors is not limited to diabetic CKD [18]. These big studies are in agreement with the reduction in albuminuria that we observed. Albuminuria is a well-proven surrogate endpoint of kidney injury, and the 30% or more reductions as observed in our treatment group are similar to the 30% or more reductions in DAPA CKD studies and with other SGLT2 inhibitor studies [19]. This similarity implies that other mechanisms, other than glucose reduction, including decreases in intraglomerular pressure and renal hemodynamic changes, are at the center stage of kidney protection. In fact, mechanistic study points out that SGLT2 inhibitors decrease glomerular hyperfiltration and stimulate desirable hemodynamic and anti-fibrotic pathways, which enable delaying the disease progression [20]. Another critical outcome of our trial, blood pressure reduction, has also been documented in several real-world and clinical studies where SGLT2 inhibitors form part of small yet clinically significant changes in systolic blood pressure, which is a significant determinant of CKD disease [21]. This hemodynamics supplement the renin angiotensin system blockade that the majority of CKD patients undergo, with synergistic potential in their combination in guideline-directed therapy [22]. Safety is stronger through comparison with previous studies; recent pooled analyses indicate that SGLT2 inhibitors do not substantially increase serious adverse events, but may potentially decrease the risk of acute kidney injury, also supporting their regular usage [23]. Also, there are non-renal advantages in the form of decreasing hospitalizations with heart failure and cardiovascular deaths reported in these studies, which gives a holistic benefit that is consistent with our findings of fewer heart failure and cardiovascular events in the treatment group [24].Other drawbacks notwithstanding, long-term durability beyond the normal 23 years of follow-up is yet to be clearly established, and the effects in cases of advanced CKD (eGFR <20 mL/min/1.73 m 2) [23]. To sum up, our results are in line with modern evidence that SGLT2 inhibitors significantly delay the development of CKD and renal and cardiovascular outcomes in non diabetic patients, which supports their growing role in CKD treatment [25].

Limitations

The limitation of the study is that the length of time (12 months) is relatively short to observe long-lasting effects or negative events. Also, the single-center structure and lack of heterogeneity of the subject group (non-diabetic CKD patients) can reduce the applicability of the results to more heterogeneous or progressive CKD groups.

CONCLUSION

Ketitolithasters can prevent CKD progression in non-diabetic patients, which is related to improved eGFR, decreased albuminuria, and decreased blood pressure. The findings justify the wider application of SGLT2 inhibitors in the treatment of CKD and emphasize their positive potential in deferring the use of dialysis and enhancing the renal and cardiovascular outcomes.

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